

# Opportunistic Infections

Developed by

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## **Note to Instructors**

This workbook is divided into four sections:

- A. Introduction to the POPS System, introduction to and objectives of the clinical simulation, and a pretest
- B. Color-coded booklets with pretest answers and the clinical problem
- C. Posttest
- D. Posttest answers

Each student should receive a copy of the first section to study and answer questions before the group problem- solving session. If you wish, the second section also may be distributed for the students to review prior to the group session.

# Opportunistic Infections

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## Pretest

**Instructions:** Please mark your answers to the following questions on this exam to facilitate later discussion and review. If your instructor has provided a separate answer form, please be sure to fill in the identification section; then answer the questions both on the form and on this exam.

Choose the *one* correct or most appropriate answer. If you do not know an answer, leave it blank. Do not guess. Health professionals who think they know something, but don't, can do real harm. Those who *know* they don't know something can get help.

Don't be upset if you don't know all the answers. The purpose of the pretest and objectives is to alert you to important concepts. The posttest will be similar to the pretest.

1. A 9-month-old baby has suffered from chronic diarrhea and diaper rash during the past six months. Fecal cultures have been negative for common enteropathogens and *Candida albicans* was repeatedly isolated. During an investigation of this child's immune response a battery of skin tests with antigens of common pathogens was applied. Six hours after intradermal inoculation of *C. albicans* antigen (candidin) a wheel and flare reaction was visible at the point of injection. The area of redness had a diameter of 12 mm, was edematous, slightly painful, but definitely not indurated. The pathogenesis of this reaction is best explained by:
  - A. Activation of granulocytes by immune complexes formed between candidin and pre-formed antibody
  - B. Degranulation of mast cells with receptor-bound IgE anti-*C. albicans* antibody
  - C. Formation of circulating complement-fixing immune complexes and deposition in the dermo-epidermal junction of the affected area
  - D. Release of IL-8 and other cytokines by activated T lymphocytes recognizing processed peptides derived from candidin
  - E. Release of inflammatory peptides from *C. albicans* organisms lysed by CD8+ T lymphocytes
2. Which one of the listed fungi would be least likely to cause a life-threatening infection?
  - A. *Trichophyton mentagrophytes*
  - B. *Candida albicans*
  - C. *Paracoccidioides brasiliensis*
  - D. *Blastomyces dermatitidis*
  - E. *Coccidioides immitis*
3. Disseminated cryptococcal infection is most common in which of the following conditions?
  - A. Acquired Immunodeficiency Syndrome
  - B. Congenital agammaglobulinemia
  - C. Extensive skin burns
  - D. IgA deficiency
  - E. Neutropenia

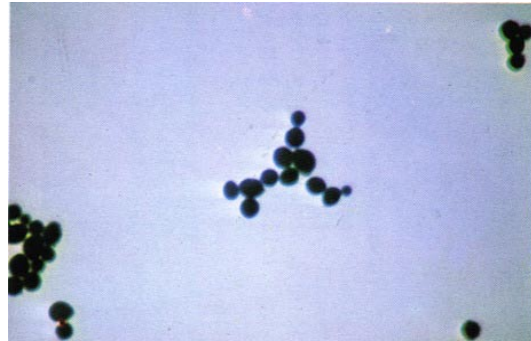
## Opportunistic Infections

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### Pretest (ctd.)

4. A 56-year-old man receiving chemotherapy for metastatic prostate carcinoma develops persistent fever not affected by administration of broad-spectrum antibiotics. A CBC and differential reveals profound neutropenia and a white exudate is seen in the vitreous of the right eye. The organism shown in the figure was grown from the peripheral blood in Sabouraud's agar. This patient's blood has been invaded by:

- A. *Aspergillus fumigatus*
- B. *Candida albicans*
- C. *Coccidioides immitis*
- D. *Cryptosporidium*
- E. *Malassezia furfur*



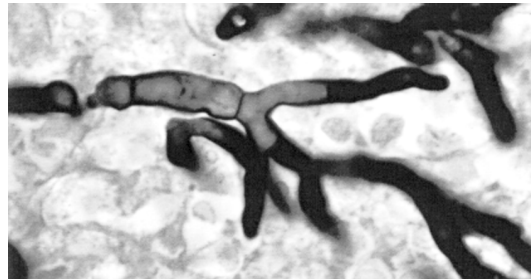
5. A 14-month-old girl has been suffering from recurrent subcutaneous abscesses since 3 months of age. Cultures have been repeatedly positive for coagulase-negative *Staphylococcus*. Physical examination shows hepatosplenomegaly and generalized lymphadenopathy. A draining abscess is present on the left side of the neck. Serum immunoglobulin levels show increases of IgG and IgM and normal IgA levels. A nitroblue tetrazolium reduction test using IgG-opsonized particles as stimulus was negative. Which of the following mechanisms is likely to be responsible for this patient's form of immunodeficiency?
- A. Inability to fuse granules with phagosomes in phagocytic cells
  - B. Inability to ingest opsonized particles
  - C. Inability to produce anti-*Staphylococcus* antibodies
  - D. Lack of expression of Fc receptors
  - E. Lack of transport of electrons to the phagolysosomes
6. At the age of four months, a boy with a normal history and family history, suddenly fell ill with a life-threatening *Pneumocystis carinii*-pneumonia. A CBC showed neutropenia and normal lymphocyte levels. Serum immunoglobulin levels showed: IgG: 200 mg/dL; IgA: 6 mg/dL; IgM: 1100 mg/dL; Isoagglutinin A titer: 16; Response to tetanus toxoid: 0 U pre-booster; 0.01 U post-booster; CD3<sup>+</sup> lymphocytes in peripheral blood: 800/ $\mu$ L; CD19<sup>+</sup> lymphocytes in peripheral blood: 98/ $\mu$ L; PHA stimulation of lymphocytes: 10,000  $\pm$  2,500 cpm of [<sup>3</sup>H]-Tdr incorporation; PWM stimulation of lymphocytes: release of 3  $\mu$ g of IgM/ $10^6$  cells at day 7; no IgG detected. The molecular basis for this condition is a deficiency of:
- A. Adenosine deaminase (ADA)
  - B. Bruton's protein kinase (Btk)
  - C. CD3-TcR complex
  - D. CD40 ligand (gp39)
  - E. Cytochrome C

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### Pretest (ctd.)

7. A newborn infant appeared septic. Blood cultures revealed a Gram positive coccobacillus, which was faintly beta hemolytic on sheep blood agar and grew well at 4°C. As the child got progressively worse, a spinal tap was performed and the Gram stain revealed similar organisms. This pathogen is most likely:
- A. Group B *Streptococcus*
  - B. *Haemophilus influenzae*
  - C. *Listeria monocytogenes*
  - D. *Neisseria meningitidis*
  - E. *Staphylococcus aureus*
8. A 30-year-old male homosexual, is seen with complaints of dysphagia and a 10-pound weight loss in the last four months. Physical examination shows white plaque lesions in the oral cavity and enlarged cervical lymph nodes. He had been found to be HIV positive four years earlier. A study of immune parameters showed polyclonal hypergammaglobulinemia, a CD4+ lymphocyte count of 40/mm<sup>3</sup> in the peripheral blood, and negative skin test to a *Candida albicans* antigen. The lack of response to *Candida* may result from:
- A. Blocking of the CD4 molecule in helper cells by soluble gp120
  - B. Depletion of helper T cells below critical levels
  - C. Emergence of AZT-resistant mutant strains of HIV in infected patients
  - D. Excessive release of IL-12 by infected macrophages
  - E. Infection of dendritic cells
9. The organism shown in the figure was visualized in the sputum of an immuno-compromised patient.



This organism is most likely a member of which of the following families?

- A. Aspergillus
  - B. Histoplasma
  - C. Madurella
  - D. Rhizopus
  - E. Sporothrix
10. The anti-mycotic effect of imidazoles is based on the inhibition of:
- A. Sterol incorporation in cell membranes
  - B. Peptidomannan cross linking
  - C. mRNA translation
  - D. Ergosterol metabolism
  - E. Microtubule assembly at the time of cell division

**When you have completed the pretest, consult your study materials. Try to identify the correct answers and understand the concepts that make them correct. The list of objectives may be used as a guideline for your studies. When your group meets, you will have the responsibility of explaining some of the correct pretest answers to the others. Please bring your textbook and pretest to the group meeting.**

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## BOOK A

**Note to Students** The fundamental purpose of all activities in the health-care professions is to help other people. Like all behavior, helping behavior becomes more effective and natural with practice. This workbook enables you to practice by helping your fellow students to learn basic science. Your skill at helping your fellow students should relate to your ability to help your patients in the future. This is a *Patient-Oriented Problem-Solving ("POPS")* workbook designed for four students. Before beginning this session, you should have (a) studied the objectives designed to prepare you for it, (b) taken the pretest, and (c) reviewed the topics listed at the end of the pretest. Now, each of you should take one of the four color-coded booklets and follow the directions in it. If your group has only three students, one of you should take two booklets. Leave the remainder of the workbook intact until you are given further instructions.

# **Opportunistic Infections**

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## **Introduction to the Patient-Oriented Problem-Solving (POPS) System**

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# Opportunistic Infections

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## Introduction

This clinical Simulation deals with opportunistic infections, which affect immunocompromised patients. A variety of organisms can infect immunocompromised patients, including bacteria, viruses, fungi, and parasites. Fungi are particularly important in this respect, because they have limited pathogenicity in a host with normal immunity.

When you have completed this activity you should be able to

- 1) define and give several examples of **opportunistic microorganisms**.
- 2) describe how different **degrees of immunocompromise** predispose to different **types of opportunistic infections**.
- 3) describe the **predisposing factors** for the development of **opportunistic mycoses**.
- 4) list **anti-mycotic agents** and their **mechanisms of action**.
- 5) List **epidemiological clues** important for the diagnosis of opportunistic infections.
- 6) list the steps involved in the **investigation** of the degree of **immunocompetence** in a patient with an opportunistic mycotic infection.
- 7) list the steps involved in the **laboratory diagnosis** of a systemic mycotic infection.
- 8) select the appropriate **treatment and prophylaxis** for the most common **opportunistic mycotic infections**.

When you **have become familiar with the objectives, complete the pretest on the next page**.

## Opportunistic Infections

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### Pretest Correct Answers

You have the answers to some of the ten pretest questions, and other members of your group have the remainder. This arrangement is designed to encourage all members of your group to actively exchange ideas and concepts. First, study the answers in your booklet and then EXPLAIN them to your group. Please don't just read them to your classmates, and don't let your classmates read their answers to you. In explaining something to another person, most people gain a better understanding of it and often transmit a better understanding. *The pretest discussion and patient-oriented problem-solving parts of this activity are "open book."* Be sure to refer to textbooks, notes, and other written resources whenever questions arise.

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1. The answer is **A**. The timing and characteristics of the skin reaction elicited by candidin are characteristic of an Arthus reaction. This type of hypersensitivity reaction is elicited when antigen is injected to a sensitized individual, which has circulating IgG antibodies to that antigen. As the antigen is injected subcutaneously, it reacts with IgG antibody pre-existing in the extravascular compartment. Antigen-antibody complexes are formed which activate complement. C5a generated as a consequence of complement activation attracts neutrophils to the site of injection. The neutrophils, which express FcγR-II and III interact with the antigen-antibody complexes, and, are consequently activated. The combined vasodilator effects of C5a, PAF, and a variety of metalloproteinases released by activated neutrophils are responsible for the reaction.
2. The answer is **A**. *Tricophyton* sp. are dermatophytes which cause skin infections and very exceptionally may cause a disseminated, life-threatening infection.
3. The answer is **A**. The arm of the immune system predominantly involved in defense against mycotic infections is cell-mediated immunity. Of the listed conditions, only the Acquired Immunodeficiency Disease is associated with a well-defined deficiency of cell-mediated immunity.

When your **group** has finished discussing the pretest, you should read the **"Instructions for the Clinical Problem"** on the next page of your booklet.



## Opportunistic Infections

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### Instructions for the Clinical Problem

Opportunistic infections are becoming more and more common due to the prevalence of diseases and medical interventions associated with a secondary depression of the immune system. The purpose of this exercise is to allow you to apply your knowledge of opportunistic infections to a clinical case that can be encountered as part of your professional life.

Each of the four group members has different sections of a case history. First, deal with your own section. After sharing the information given to each one of you by the prescribed order, decide the next steps you would take, discuss the reasons for your choice(s) - group members who disagree with a given choice, the reasons for it, or consequences of it should present their ideas and defend them. The final group answers should be recorded in the handouts. After you reach the end of the case you should revisit it and make sure that all the answers make sense and that no one in the group is left with unanswered questions or misconceptions.

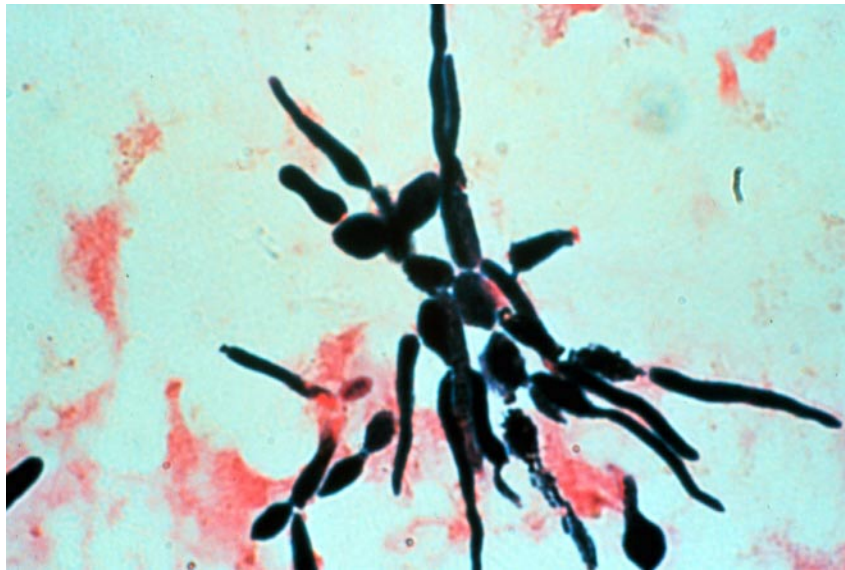
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## Opportunistic Infections

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### Mrs. Johnson: Initial encounter (1990)

Mrs. Johnson is a 32-yr. old white female, who sought medical help because she noticed a thick, white vaginal discharge associated with perineal itching and discomfort. A Gram stain of the exudate was obtained:



Describe the structure demonstrated in this Gram stain

What is your diagnosis?

Could you demonstrate this organism by any other type of procedure?

Should you order a culture?

What treatment would you recommend? What is the mechanism of action of your drug of choice?

Are there any therapeutic alternatives to your drug of choice?

## Opportunistic Infections

### Correct answers to Mrs. Johnson Initial encounter

Describe the structure demonstrated in this Gram stain

*The picture shows yeast cells with pseudohyphae*

What is your diagnosis?

*The visualization of yeast cells with pseudohyphae in the vaginal discharge is diagnostic of vaginal candidiasis*

Could you demonstrate this type of organism by any other type of procedure?

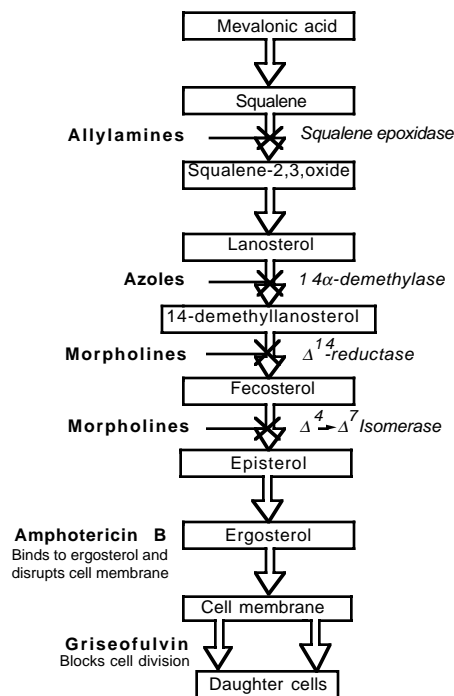
*Most yeasts and fungi can be easily visualized with a KOH preparation*

Should you order a culture?

*Not necessary in this case. Cultures and antifungal susceptibility studies are usually reserved for cases in which the disease is widespread and there is reason to be concerned about resistance.*

What treatment would you recommend? What is the mechanism of action of your drug of choice?

*A single 150 mg oral dose of fluconazole should be effective. The azoles block ergosterol synthesis. As shown in the diagram below, this is achieved by blocking 14 $\alpha$ -demethylase, which prevents the conversion of lanosterol into 14-demethyl lanosterol.*



Are there any therapeutic alternatives to your drug of choice?

Oral ketoconazole 200 mg/day, for three days; a variety of topical preparations for intravaginal application are also available. Many of these are available over the counter.

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4. The answer is **B**. Patients with neutropenia are at special risk of developing systemic candidiasis. The white exudate seen in the vitreous of the right eye is considered diagnostic of systemic candidiasis (the exudate is a mass of *C. albicans*). The isolation of *C. albicans* from the peripheral blood, as shown in the picture confirms the diagnosis.
5. The answer is **E**. The clinical history and PE finding are suggestive of a congenital phagocyte deficiency, and the negative results of the nitroblue tetrazolium test point towards a diagnosis of chronic granulomatous disease. This disease is frequently (but not exclusively) X-linked and is caused by the deficiency of one of four genes whose products are required to form an active NADPH oxidase and to transport electrons into the phagolysosome. Such transport is required to convert oxygen into superoxide, initiating the oxidative burst, which is probably the most important killing mechanism in phagocytic cells.

## Opportunistic Infections

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Opportunistic infections are becoming more and more common due to the prevalence of diseases and medical interventions associated with a secondary depression of the immune system. The purpose of this exercise is to allow you to apply your knowledge of opportunistic infections to a clinical case that can be encountered as part of your professional life.

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## Opportunistic Infections

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### **Mrs. Johnson: Past history and follow up**

The patient's physician diagnosed vaginal candidiasis, and the patient was treated with a single dose of oral fluconazole, with immediate resolution of all signs and symptoms.

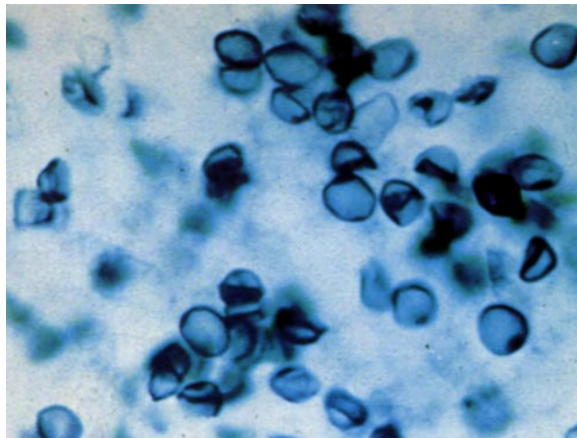
Past history for this patient was unremarkable. She had been generally healthy. She had been hospitalized once after being involved in an auto accident in December 1984. She had minimal injuries but her husband had a ruptured spleen and had required transfusions and surgery for splenectomy.

Over the subsequent three years after the initial encounter Mrs. Johnson experienced four additional episodes of vaginal yeast infection, none of which were associated with prior use of broad-spectrum antibiotics. All episodes resolved with fluconazole treatment following the same protocol as in the first episode.

What medical conditions predispose to opportunistic mycoses?

### **Mrs. Johnson has a baby**

In 1995 the patient became pregnant and delivered a healthy nine-pound male child, with a normal Apgar score, after an uneventful pregnancy. The child remained well until 1997, when he was hospitalized with fever and shortness of breath. Blood cultures were negative. A chest X-ray showed bilateral infiltrates suggestive of interstitial pneumonia. A bronchoalveolar lavage was performed and the following organisms were observed in a smear of the lavage sediment with methenamine-silver.



What was the most likely diagnosis for this child's respiratory infection?

How would you treat this child's disease?

Would you perform additional tests on this child and his parents?

## Opportunistic Infections

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### Correct answers to Mrs. Johnson: Past history and follow up

What medical conditions predispose to opportunistic mycoses?

*Opportunistic mycoses are frequent in patients with diabetes, neutropenia (total neutrophil count  $<100/\mu\text{L}$ ), and primary or secondary deficiencies in cell-mediated immunity (total CD4 count  $<400/\mu\text{L}$ ). Patients with hematological malignancies are predisposed by virtue of the functional incompetence of the malignant cells and by the severe compromise of their immune system associated with chemotherapy (neutropenia in particular). Neutropenia and depression of cell-mediated immunity are also common in patients receiving immunosuppressive therapy after organ transplantation. Finally, virtually all AIDS patients will suffer from one or another fungal infection at some time during the course of their disease.*

What was the most likely diagnosis for this child's respiratory infection?

*The picture reproduces the typical morphological characteristics of *Pneumocystis carinii*. Therefore, a diagnosis of *Pneumocystis carinii* pneumonia was established.*

How would you treat this child's disease?

*The current treatment of *Pneumocystis carinii* pneumonia includes intravenous administration of sulfamethoxazole-trimethoprim and supportive measures to improve the level of oxygenation of blood circulating through the lungs.*

Would you perform additional tests on this child and his parents?

*The diagnosis of *Pneumocystis carinii* pneumonia in a young child should lead to the investigation of possible immunodeficiency. Phagocytic cell number and function, as well as cell mediated immunity should be investigated. Given the prevalence of AIDS, the child and his parents should be tested for HIV antibodies.*

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6. The answer is **D**. The onset of opportunistic infections at a very young age always suggests a congenital immunodeficiency. In this case, the child has low IgG and IgA and very high IgM. His response to immunization with DT is weak, but his total T and B cell counts are normal and the response to mitogenic stimulation seems adequate. However, pokeweed mitogen-stimulated B-lymphocytes produce IgM but not IgG. Overall, these findings suggest a diagnosis of hyper-IgM syndrome, which is due to lack of expression of gp39 (CD40 ligand). The signals mediated by interaction of CD40 with its ligand appear to be critical for B cell switch from IgM synthesis to the synthesis of immunoglobulins of other isotypes.
7. The answer is **C**. Neonates can be considered as mildly immunocompromised, and as such more likely to develop infections with low-grade pathogens. The list of bacteria associated with neonatal meningitis included group B streptococcus, *Escherichia coli*, and *Listeria monocytogenes*. Of these organisms, *L. monocytogenes* corresponds to the description given in the question - Gram positive coccobacillus, faintly beta hemolytic on sheep blood agar, which grows at low temperatures.

## Opportunistic Infections

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### Instructions for the Clinical Problem

Opportunistic infections are becoming more and more common due to the prevalence of diseases and medical interventions associated with a secondary depression of the immune system. The purpose of this exercise is to allow you to apply your knowledge of opportunistic infections to a clinical case that can be encountered as part of your professional life.

Each of the four group members has different sections of a case history. First, deal with your own section. After sharing the information given to each one of you by the prescribed order, decide the next steps you would take, discuss the reasons for your choice(s) - group members who disagree with a given choice, the reasons for it, or consequences of it should present their ideas and defend them. The final group answers should be recorded in the handouts. After you reach the end of the case you should revisit it and make sure that all the answers make sense and that no one in the group is left with unanswered questions or misconceptions.

*Remember, this is an "open-book" activity, and you should consult your textbooks about any point you don't understand.*

## Opportunistic Infections

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### Mrs. Johnson: Aftermath

The child was diagnosed with *Pneumocystis carinii* pneumonia and was treated with trimethoprim-sulfamethoxazole. Mrs. Johnson, her husband, and child were found to be HIV positive by ELISA and confirmatory Western blot analysis. The CD4 count in the husband was 154 cells/mm<sup>3</sup>, with an HIV load of 42,000-copies/ cm<sup>3</sup>. Mrs. Johnson was found to have a CD4 count of 380 cells/mm<sup>3</sup>, with an HIV viral load of 5,000 copies/cm<sup>3</sup>.

How are the serological tests for HIV conducted?

What is the methodology used for determination of the viral load?

Can you trace down the source of infection for this couple and their baby?

What therapy would you prescribe to the members of this family?

Are there any special considerations that you need to keep in mind if this patient becomes infected again with *Candida albicans* while receiving High Activity Anti-Retroviral therapy (HAART)?

Are there any other gynecological conditions to be investigated in Mrs. Johnson?




## Opportunistic Infections

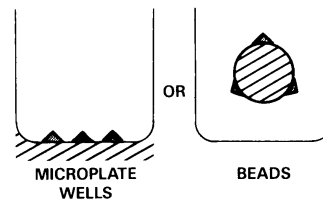
### Correct answers to Mrs. Johnson: Aftermath


How are the serological tests for HIV conducted?

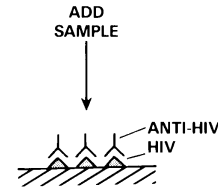
*HIV antibodies are screened by enzymeimmunoassay. The principle of the assay is illustrated in the diagram below.*


### Diagrammatic Representation of an EIA Assay for HIV Antibodies

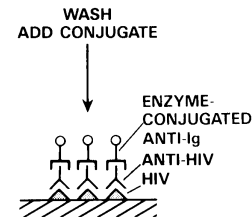
Partially purified, inactivated human immunodeficiency virus (HIV) (antigen,  $\Delta$ ) is absorbed on microplate wells or polystyrene beads (solid phase, .




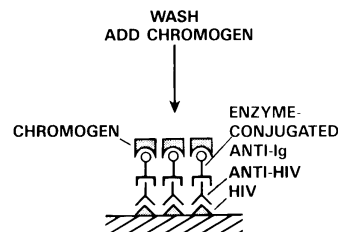
Samples to be tested are added, incubated with the HIV antigen, and washed. HIV-specific antibodies () , if present, bind to absorbed antigens and are not removed by washing.



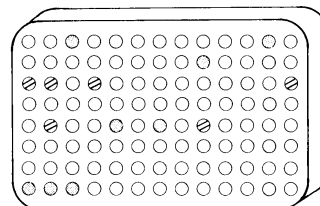
Enzyme-conjugated anti-human immunoglobulin (anti-Ig) () binds to anti-HIV.



Chromogen () develops color in proportion to quantity of enzyme-conjugated Ig.



Chromogen reaction is stopped. Optical absorbance is read by spectrophotometer, and test results are interpreted by relating optical density to cut-off value established by controls.

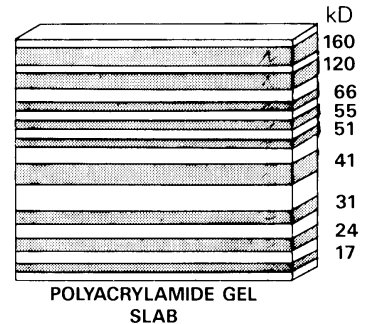


Reproduced from Sandler et al., Diagnostic Tests for HIV Infection: Serology. In AIDS (2nd Ed.), De Vita, Hellman & Rosenberg, Eds. P. 121, Lippincott 1988.

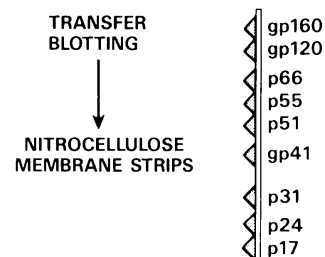
If The EIA for HIV antibody is repeatedly positive, the result is the verified by Western Blot analysis. The following diagram illustrates the principle of a Western Blot for HIV antibody.

### Diagrammatic Representation of a Western Blot Assay for HIV Antibodies

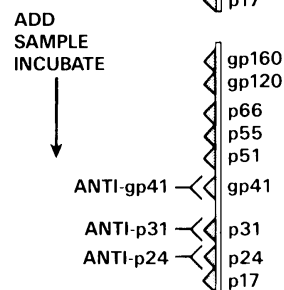
Disrupted, partially purified human immunodeficiency virus (HIV) is fractionated by polyacrylamide gel electrophoresis, distributing viral components according to molecular weight expressed in kilodaltons (kD).



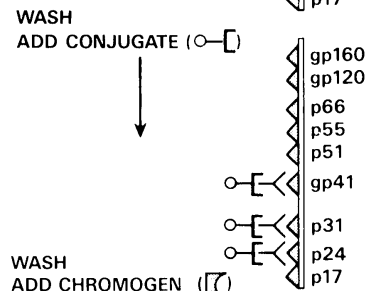
HIV proteins (p) and glycoproteins (gp) are transferred to nitrocellulose membranes, which are cut into individual strips. HIV proteins and glycoproteins function as specific antigens (◁).



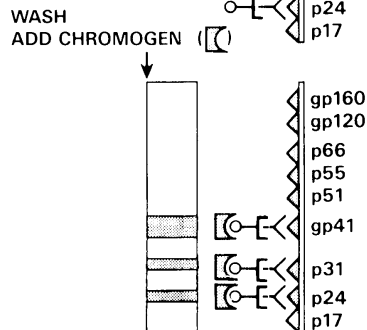
Nitrocellulose strips are incubated with serum or plasma, binding HIV-specific antibodies (—>), if present, to corresponding antigens.



Enzyme-conjugated anti-human immunoglobulin binds to strips in areas that correspond to antibody-antigen reactions.



Added chromogen develops color and stains strips in bands that correspond to distribution of antibody-antigen reactions.

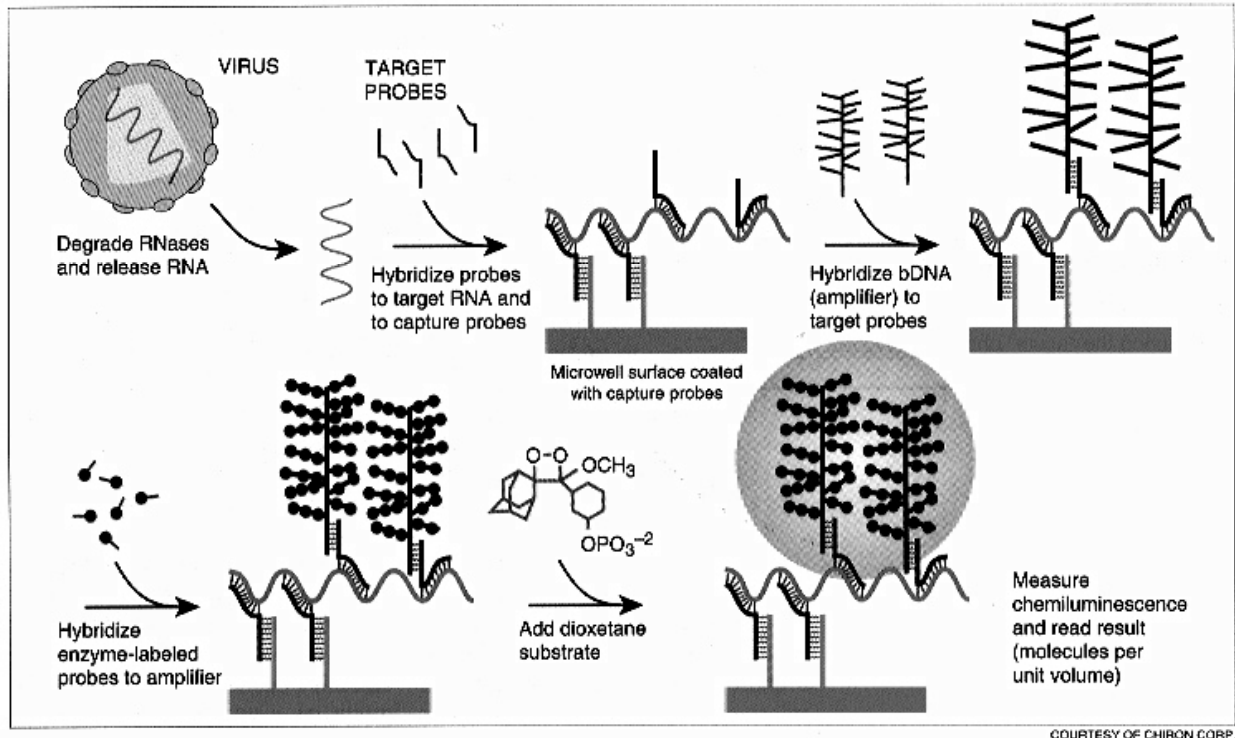


Reproduced from Sandler et al., Diagnostic Tests for HIV Infection: Serology. In AIDS (2nd Ed.), De Vita, Hellman & Rosenberg, Eds. P. 121, Lippincott 1988.

What is the methodology used for determination of the viral load?

*The viral load can be determined by a variety of assays. The branched DNA assay is one of the most used techniques:*

### Branched DNA assay for HIV RNA



Can you trace down the source of infection for this couple and their baby?

*Mrs. Johnson was hospitalized once after being involved in an auto accident in December 1984. She had minimal injuries but her husband had a ruptured spleen and had required transfusions and surgery for splenectomy. At that time the blood supply was not safe, and Mrs. Johnson's husband, who was obviously infected, may have acquired HIV by transfusion. Obviously, this is only an hypothesis, which would require confirmation by excluding other possible routes of transmission (sexual contact, intravenous drug use) and tracking back the source of the blood that Mr. Johnson received.*

What therapy would you prescribe to the members of this family?

*At this time, most physicians who specialize in the treatment of HIV infections would recommend that all members of the family receive High Activity Anti-Retroviral therapy (HAART). This usually involves the administration of three different anti-retroviral drugs, most often two anti-reverse transcriptase inhibitors and a protease inhibitor. Such associations are not made randomly, there are recommended protocols to be followed. Not all antiretrovirals are available in pediatric formulations, but most of the nucleotide analogue RT inhibitors and protease inhibitors are available. The following are combinations frequently used in children:*

- ZDV + 3TC + Nelfinavir
- ZDV + 3TC + Ritonavir
- D4T + DDI + Nelfinavir
- D4T + DDI + Ritonavir
- D4T + 3TC + Nelfinavir
- D4T + 3TC + Ritonavir
- ZDV + 3TC + Nevirapine
- D4T + 3TC + Nevirapine
- D4T + DDI + Nevirapine

Are there any special considerations that you need to keep in mind if this patient becomes infected again with *Candida albicans* while receiving High Activity Anti-Retroviral therapy (HAART)?

*The main consideration is drug interactions. Most protease inhibitors and azole antifungals inhibit the cytochrome P450 system, and, therefore, their co-administration may result in higher blood levels and toxicity. Of the protease inhibitors Ritonavir is the most likely to cause problems when given at the same time as another drug catabolized by the P450 cytochrome system. Of the azoles, ketoconazole is the most likely to cause problems. Fluconazole (Diflucan®) is associated with less drug interactions when dosages of 200 mg/day or less are used.*

Are there any other gynecological conditions to be investigated in Mrs. Johnson?

*HIV-infected patients have a higher incidence of cervical carcinoma associated with papilloma viruses.*

# Opportunistic Infections

Developed by

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## BOOK D

**Note to Students** The fundamental purpose of all activities in the health-care professions is to help other people. Like all behavior, helping behavior becomes more effective and natural with practice. This workbook enables you to practice by helping your fellow students to learn basic science. Your skill at helping your fellow students should relate to your ability to help your patients in the future. This is a *Patient-Oriented Problem-Solving ("POPS")* workbook designed for four students. Before beginning this session, you should have (a) studied the objectives designed to prepare you for it, (b) taken the pretest, and (c) reviewed the topics listed at the end of the pretest. Now, each of you should take one of the four color-coded booklets and follow the directions in it. If your group has only three students, one of you should take two booklets. Leave the remainder of the workbook intact until you are given further instructions.

# **Opportunistic Infections**

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## **Introduction to the Patient-Oriented Problem-Solving (POPS) System**

This is a Patient-Oriented Problem-Solving activity. The purposes are

1. To help you learn how to apply your basic science knowledge to the solution of clinical problems
2. To help you learn how to better use sources (i.e., textbooks and peers) that will be available to you throughout your career
3. To help you work with your fellow students and thus
  - a. increase your ability to evaluate your colleagues' opinions, thought processes, and diagnoses
  - b. increase communications skills
  - c. get to know your classmates better

This activity consists of four phases. First, you will review the attached set of objectives, do background reading on the topics to be covered, and complete the pretest on your own. In the second phase, you will join three other students and review the pretest answers in an "open-book" discussion. In the third phase, the group will solve patient-oriented problems. Information exchange and group interaction are keys to the success of this phase. This process will allow you to teach your fellow students and, at the same time, learn from them. Finally, you will take a post-test, individually, which will enable you to assess your progress.

# Opportunistic Infections

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## Introduction

This clinical Simulation deals with opportunistic infections, which affect immunocompromised patients. A variety of organisms can infect immunocompromised patients, including bacteria, viruses, fungi, and parasites. Fungi are particularly important in this respect, because they have limited pathogenicity in a host with normal immunity.

When you have completed this activity you should be able to

- 1) define and give several examples of **opportunistic microorganisms**.
- 2) describe how different **degrees of immunocompromise** predispose to different **types of opportunistic infections**.
- 3) describe the **predisposing factors** for the development of **opportunistic mycoses**.
- 4) list **anti-mycotic agents** and their **mechanisms of action**.
- 5) List **epidemiological clues** important for the diagnosis of opportunistic infections.
- 6) list the steps involved in the **investigation** of the degree of **immunocompetence** in a patient with an opportunistic mycotic infection.
- 7) list the steps involved in the **laboratory diagnosis** of a systemic mycotic infection.
- 8) select the appropriate **treatment and prophylaxis** for the most common **opportunistic mycotic infections**.

When you **have become familiar with the objectives, complete the pretest on the next page**.

## Opportunistic Infections

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### Pretest Correct Answers

You have the answers to some of the ten pretest questions, and other members of your group have the remainder. This arrangement is designed to encourage all members of your group to actively exchange ideas and concepts. First, study the answers in your booklet and then EXPLAIN them to your group. Please don't just read them to your classmates, and don't let your classmates read their answers to you. In explaining something to another person, most people gain a better understanding of it and often transmit a better understanding. *The pretest discussion and patient-oriented problem-solving parts of this activity are "open book."* Be sure to refer to textbooks, notes, and other written resources whenever questions arise.

You will probably want to make notes on your pretest to help you review questions that you missed. Avoid "collecting pages" for "later study and understanding." Learn the concepts now so that later you will only need to review them.

8. The answer is **B**. This patient is likely to have oro-esophageal candidiasis as a manifestation of AIDS. However, a skin tests with a *C. albicans* extract is negative. The reason for this negativity is most likely the marked depletion of CD4+ lymphocytes, which are essential to elicit T cell-mediated inflammatory reactions.
9. The answer is **A**. The finding of a septate filamentous fungus, which branches at approximately 45° angles, is characteristic of *Aspergillus* species..
10. The answer is **D**. Imidazoles block 14 $\alpha$ -demethylase, responsible for the conversion of lanosterol into 14-demethylallosterol, one of the several steps in the synthesis of ergosterol.



## Opportunistic Infections

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### Instructions for the Clinical Problem

Opportunistic infections are becoming more and more common due to the prevalence of diseases and medical interventions associated with a secondary depression of the immune system. The purpose of this exercise is to allow you to apply your knowledge of opportunistic infections to a clinical case that can be encountered as part of your professional life.

Each of the four group members has different sections of a case history. First, deal with your own section. After sharing the information given to each one of you by the prescribed order, decide the next steps you would take, discuss the reasons for your choice(s) - group members who disagree with a given choice, the reasons for it, or consequences of it should present their ideas and defend them. The final group answers should be recorded in the handouts. After you reach the end of the case you should revisit it and make sure that all the answers make sense and that no one in the group is left with unanswered questions or misconceptions.

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## Opportunistic Infections

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### **Mrs. Johnson: Closure**

A full evaluation of this patient was carried out after recognition of her HIV status. An abnormal Pap smear was found and colposcopy revealed an area suspicious for cervical intra-epithelial neoplasia. Evaluation for human papilloma virus within the cervico-vaginal lavage fluid confirmed presence of HPV, type 18. A loop electric excision procedure was performed. The patient was started on combination therapy with zidovudine, 3TC and saquinavir. Her viral load became undetectable and her CD4 count rose to 500 cells/mm<sup>3</sup>. The patient remained clinically well and became pregnant in the fall of 1997.

What advice should you give this woman concerning her pregnancy?

Should the antiretroviral therapy be modified during pregnancy?

If the pregnancy is allowed to follow its course, what is the risk for the baby to acquire HIV?

## Opportunistic Infections

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### Correct answers to Mrs. Johnson: Closure

What advice should you give this woman concerning her pregnancy?

*Mrs. Johnson should be made aware that standard prophylactic therapy with AZT reduces the risk of transmission to the baby and that triple therapy is likely to reduce the risk even further. She should also be advised about the potential advantages of elective C-section over natural birth and the risk associated with breast-feeding (0.5% per month of breast feeding).*

Should the antiretroviral therapy be modified during pregnancy?

*Only to the extent that if Mrs. Johnson's HAART does not include ZDV, it should be modified to include this antiretroviral drug.*

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Table 3. Guidelines for Use of Zidovudine (AZT) in Pregnancy

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During Pregnancy
AZT, 200 mg p.o. TID
Begin after 14 weeks of gestation
During Delivery
AZT, 2 mg/kg IV over 1 hr
Thereafter, AZT, 1 mg/kg by continuous infusion until delivery
Neonatal
Oral AZT syrup, 2 mg/kg q 6 h x 6 weeks
Can give AZT IV if p.o. not possible

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Note: Give AZT during delivery even if patient has had none during pregnancy.  
Give AZT to neonate even if mother has had none.

If the pregnancy is allowed to follow its course, what is the risk for the baby to acquire HIV?

*There is a risk of materno-fetal transmission from 25 – 30% when anti-retroviral therapy is not administered. The use of AZT is associated with approximately a 70% decrease in risk of HIV transmission, down to 8.3%. Triple therapy is believed to reduce the risk to  $\leq 2\%$ , but there is not hard data yet proving that this is the case. On the other hand, elective C-section has been shown to decrease the risk of transmission to about 2%.*

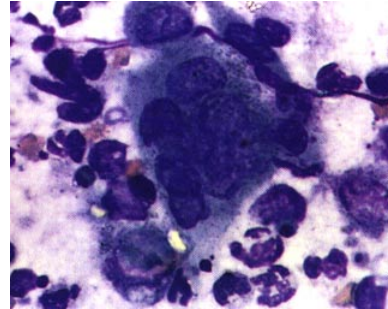
# Opportunistic Infections

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## Posttest

Select the best answer for each question. Please mark your answer on this exam to facilitate discussion and later review. If your instructor has provided a separate answer form, be sure you have identified yourself on the form, then begin your answers with question 1. Mark your answers both on the form and on this exam. Only one answer is correct.

1. A 66-year-old man under treatment for chronic lymphocytic leukemia develops a vesicular rash in the trunk. Cytological examination of scrapings from the base of one of the vesicles reveals the cells shown in the figure on the right. The virus responsible for these lesions is most likely a member of the \_\_\_\_\_ family:



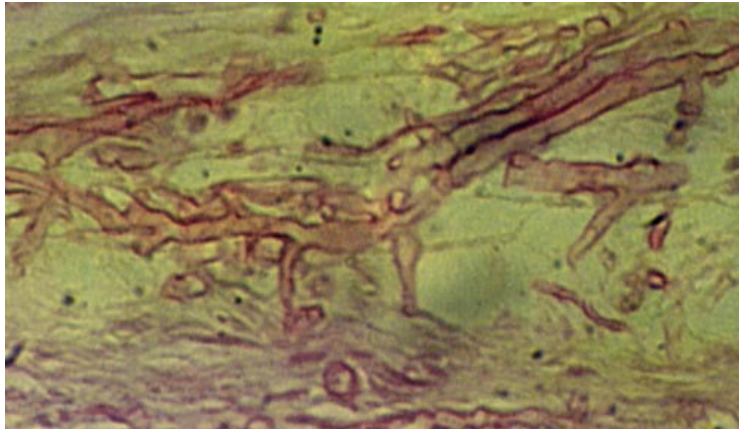
- A. Herpesvirus
  - B. Papovavirus
  - C. Paramyxovirus
  - D. Picornavirus
  - E. Retrovirus
2. All the following tests are useful in evaluating the state of a patient's cell-mediated immunity EXCEPT:
- A. Ability of lymphocytes to produce interleukin-2 in response to mitogenic stimulation
  - B. Absolute count of CD4<sup>+</sup>/CD8<sup>+</sup> lymphocytes
  - C. Incorporation of [<sup>3</sup>H] thymidine by lymphocytes stimulated with phytohemagglutinin
  - D. Incorporation of [<sup>3</sup>H] thymidine by the reactive cells on a one-way mixed lymphocyte culture
  - E. Release of Platelet Activating Factor (PAF) after incubation with opsonized latex particles
3. Which of the following fungi is most likely to spread from person to person?
- A. *Aspergillus fumigatus*
  - B. *Cryptococcus neoformans*
  - C. *Histoplasma capsulatum*
  - D. *Sporothrix shenkii*
  - E. *Trichophyton tonsurans*
4. Which of the following fungal cell components is(are) the target of most anti-mycotic drugs?
- A. Cell membrane integrity
  - B. DNA polymerases
  - C. Enzymes involved in ergosterol synthesis
  - D. Microtubules
  - E. Ribosomes

## Opportunistic Infections

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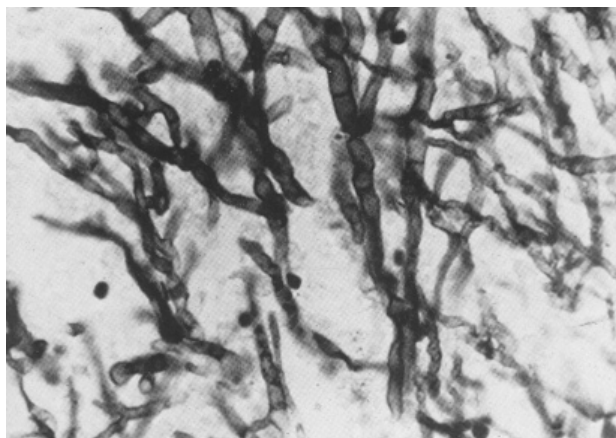
### Posttest

5. A 62-year-old diabetic woman presents with sinusitis which does not respond to antibacterial agents. Intranasal exam reveals a white cotton-like growth. A KOH preparation is obtained (see figure).



The most likely cause of this infection is:

- A. *Actinomyces israelii*
  - B. *Aspergillus fumigatus*
  - C. *Malassezia furfur*
  - D. *Rhizopus* sp.
  - E. *Streptomyces* sp.
6. A 56-year-old man receiving chemotherapy for leukemia develops a non-healing ulcer on the helix of his left ear. A CBC and differential reveals profound neutropenia. Culture of the exudate from the ulceration on Sabouraud's agar grew the organism shown in the figure. Which of the following therapeutic measures is LEAST likely to be beneficial to this patient?



- A. Administration of amphotericin B
- B. Administration of GM-CSF
- C. Buffy-coat transfusion
- D. Replacing the broad spectrum antibiotics by a new combination
- E. Suspension of cytotoxic administration

## Opportunistic Infections

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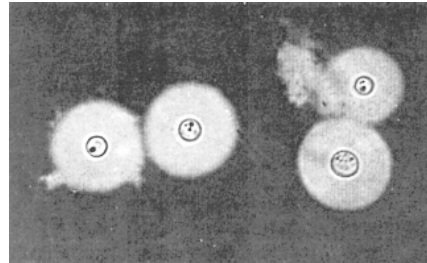
### Posttest

Questions 7 - 8 refer to the following case:

A 21-year-old Hispanic female with systemic lupus erythematosus presents with symptoms of meningitis. The CSF protein is elevated and the glucose is low. The gram stain shows no organisms. The result of an India ink preparation is shown in the figure.

7. This organism can be recovered in large quantities from:

- A. Bat guano
- B. Blackbird roosting grounds
- C. Mexican pottery
- D. Organic debris
- E. Pigeon and chicken droppings



8. The main virulence factor of this organism is its:

- A. ability to survive intracellularly
- B. anti-phagocytic capsule
- C. cell wall lipopolysaccharide
- D. poor immunogenicity
- E. resistance to most antimicrobials

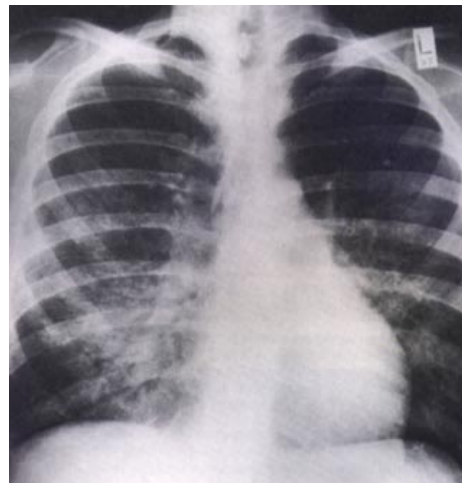
9. Which of the following anti-mycotic agents is preferred for the prevention of cryptococcal meningitis in symptomatic HIV<sup>+</sup> patients?

- A. 5-fluorocytosine
- B. Amphotericin B
- C. Fluconazole
- D. Ketoconazole
- E. Terbinafine

10. A 32-year-old Caucasian male is seen at the emergency room with shortness of breath and cyanosis. The chest X-ray is shown in the figure.

A bronchoalveolar lavage sediment stained by methenamine-silver reveals cysts with multiple spores. The patient is found to be HIV positive. Treatment of this patient's pulmonary infection should involve administration of a drug or combination of drugs which:

- A. Blocks mRNA translation
- B. Blocks the 50s ribosome
- C. Inhibits HIV replication
- D. Interferes with nucleotide synthesis
- E. Prevents peptidoglycan crosslinking



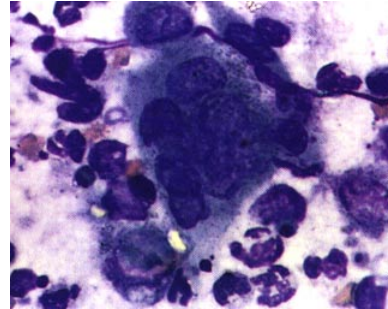
# Opportunistic Infections

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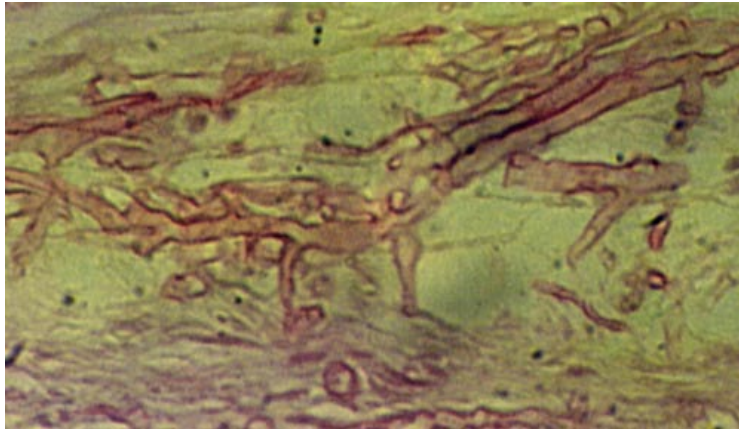
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## Opportunistic Infections

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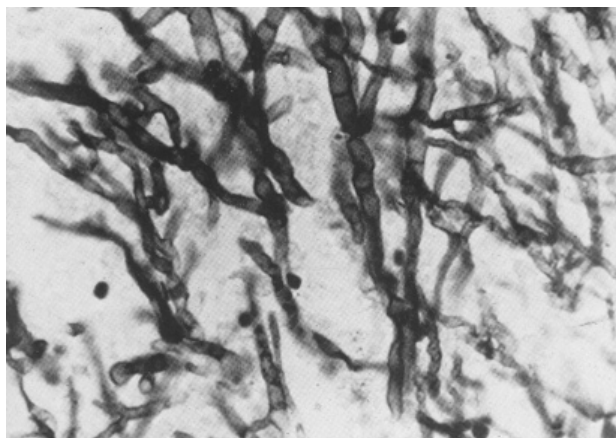
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## Opportunistic Infections

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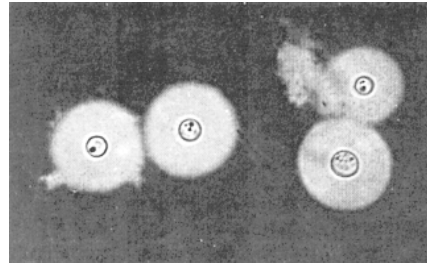
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- D. Organic debris
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8. The main virulence factor of this organism is its:

- A. ability to survive intracellularly
- B. anti-phagocytic capsule
- C. cell wall lipopolysaccharide
- D. poor immunogenicity
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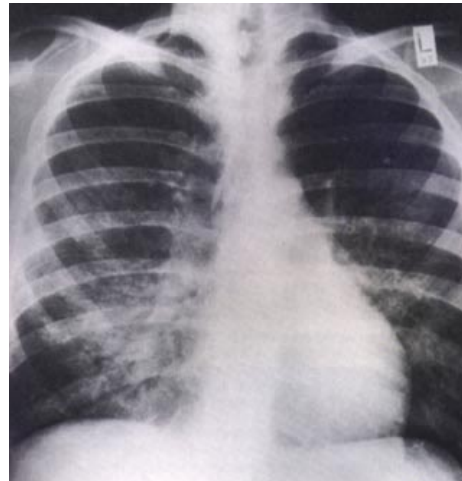
9. Which of the following anti-mycotic agents is preferred for the prevention of cryptococcal meningitis in symptomatic HIV<sup>+</sup> patients?

- A. 5-fluorocytosine
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10. A 32-year-old Caucasian male is seen at the emergency room with shortness of breath and cyanosis. The chest X-ray is shown in the figure.

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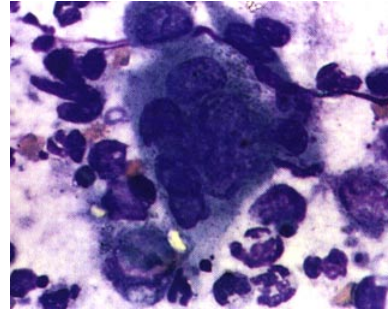
# Opportunistic Infections

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## Posttest

Select the best answer for each question. Please mark your answer on this exam to facilitate discussion and later review. If your instructor has provided a separate answer form, be sure you have identified yourself on the form, then begin your answers with question 1. Mark your answers both on the form and on this exam. Only one answer is correct.

1. A 66-year-old man under treatment for chronic lymphocytic leukemia develops a vesicular rash in the trunk. Cytological examination of scrapings from the base of one of the vesicles reveals the cells shown in the figure on the right. The virus responsible for these lesions is most likely a member of the \_\_\_\_\_ family:



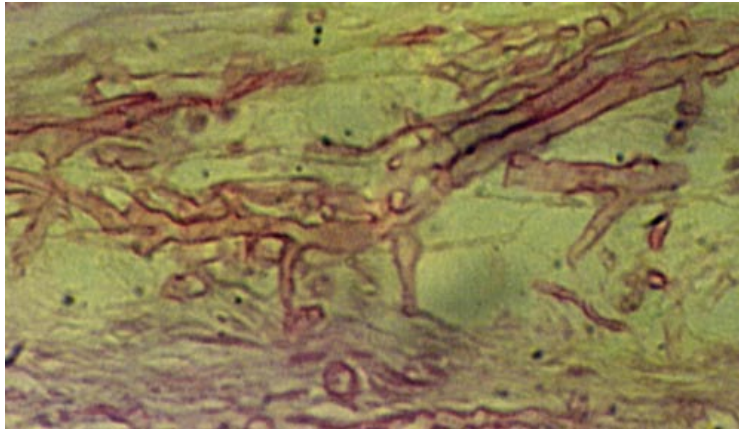
- A. Herpesvirus
  - B. Papovavirus
  - C. Paramyxovirus
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2. All the following tests are useful in evaluating the state of a patient's cell-mediated immunity EXCEPT:
- A. Ability of lymphocytes to produce interleukin-2 in response to mitogenic stimulation
  - B. Absolute count of CD4<sup>+</sup>/CD8<sup>+</sup> lymphocytes
  - C. Incorporation of [<sup>3</sup>H] thymidine by lymphocytes stimulated with phytohemagglutinin
  - D. Incorporation of [<sup>3</sup>H] thymidine by the reactive cells on a one-way mixed lymphocyte culture
  - E. Release of Platelet Activating Factor (PAF) after incubation with opsonized latex particles
3. Which of the following fungi is most likely to spread from person to person?
- A. *Aspergillus fumigatus*
  - B. *Cryptococcus neoformans*
  - C. *Histoplasma capsulatum*
  - D. *Sporothrix shenkii*
  - E. *Trichophyton tonsurans*
4. Which of the following fungal cell components is(are) the target of most anti-mycotic drugs?
- A. Cell membrane integrity
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  - D. Microtubules
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## Opportunistic Infections

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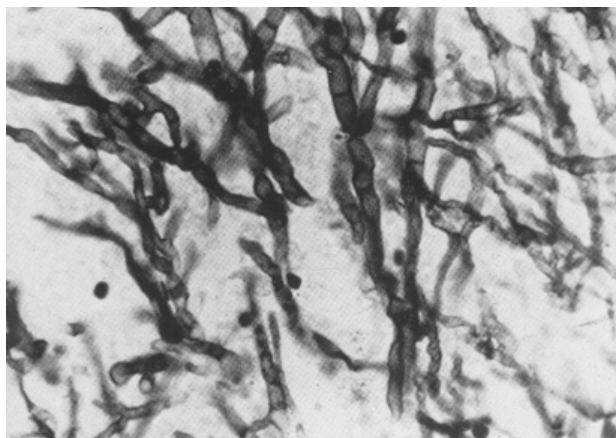
### Posttest

5. A 62-year-old diabetic woman presents with sinusitis which does not respond to antibacterial agents. Intranasal exam reveals a white cotton-like growth. A KOH preparation is obtained (see figure).



The most likely cause of this infection is:

- A. *Actinomyces israelii*
  - B. *Aspergillus fumigatus*
  - C. *Malassezia furfur*
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- A. Administration of amphotericin B
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## Opportunistic Infections

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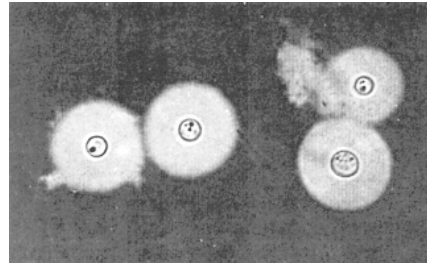
### Posttest

Questions 7 - 8 refer to the following case:

A 21-year-old Hispanic female with systemic lupus erythematosus presents with symptoms of meningitis. The CSF protein is elevated and the glucose is low. The gram stain shows no organisms. The result of an India ink preparation is shown in the figure.

7. This organism can be recovered in large quantities from:

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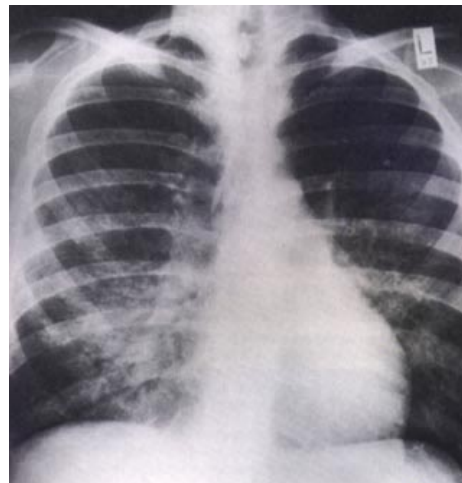
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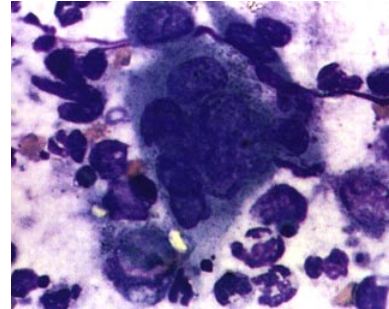
# Opportunistic Infections

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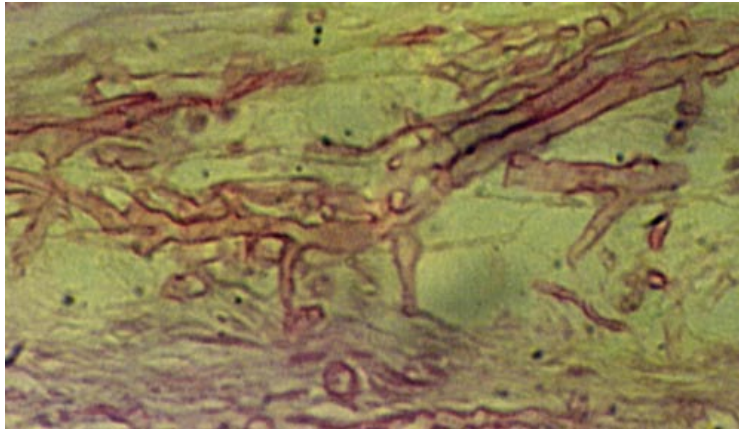


## Opportunistic Infections

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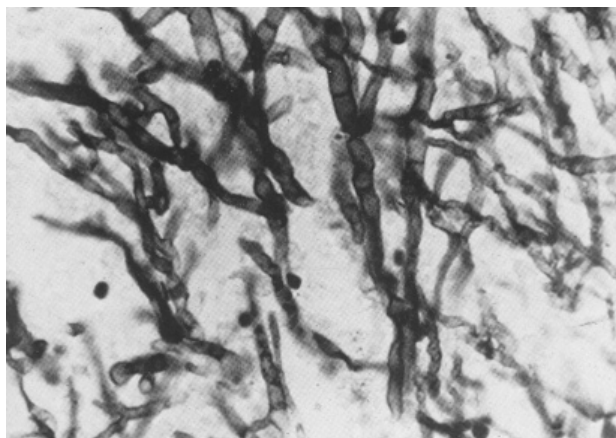
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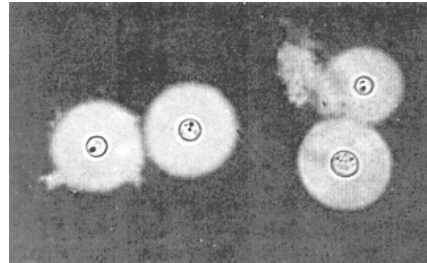
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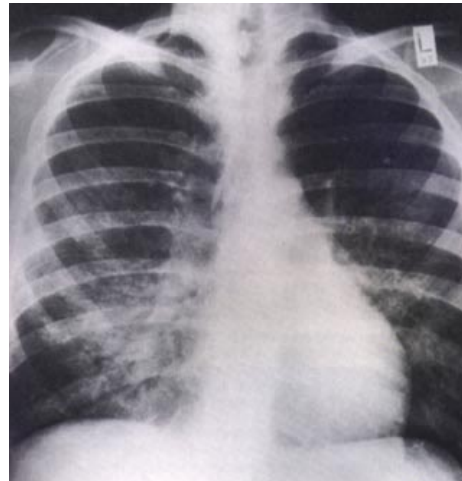
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## Opportunistic Infections

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### Posttest answers

Discuss answers with each other to be sure none of you have any misconceptions!

1. The answer is **A**. Reactivation of latent Herpes viruses infections (particularly Herpes simplex and Herpes zoster) is relatively frequent in leukemic patients receiving chemotherapy. The characteristic of the rash (vesicular) and the finding of multinucleated giant cells on scrapings from one of the vesicles strongly suggests that the Varicella zoster virus is involved.
2. The answer is **E**. All end points of the other choices are indicative of T cell numbers and/or function. In contrast, PAF is released by granulocytic phagocytes after ingestion of opsonized latex particles.
3. The answer is **E**. Most fungi are opportunistic agents acquired from the environment. The exceptions to this rule are some of the dermatophytes, which can be transmitted from person-to-person, either through contaminated utensils or by close personal contact.
4. The answer is **C**. Most antifungal agents, including the azoles, the allylamines, and the morpholines inhibit different steps of ergosterol synthesis. The polyenes (nystatin and amphotericin B) bind to ergosterol and disrupt the fungal cell membrane. 5-fluorocytosine is a nucleoside analogue, which blocks the fungal DNA polymerase and inhibits DNA and RNA synthesis. Griseofulvin blocks microtubule polymerization, and, as a consequence, inhibits the formation of the mitotic spindle and stops cell division.
5. The answer is **D**. The case scenario is strongly suggestive of mucormycosis, and this impression is confirmed by the finding broad, ribbon-like, non-septate hyphae in the KOH preparation.
6. The answer is **D**. This patient has a rare form of cutaneous aspergillosis associated with profound neutropenia, which was diagnosed on the basis of the culture. *Aspergillus fumigatus* and all other fungi are not affected by any known anti-bacterial agent, so that changing the broad-spectrum antibiotics will not have a beneficial effect. All other measures may have a positive impact - some by treating the fungal infection (amphotericin B), others for increasing granulocyte counts (GM-CSF, buffy-coat transfusion), and others by removing the cause of immunosuppression (suspension of the administration of cytotoxic drugs).
7. The answer is **E**. The visualization of an encapsulated yeast in CSF by the India ink test is diagnostic of cryptococcal meningitis, which is usually seen in immunocompromised patient. Patients with autoimmune diseases are usually immunocompromised as a result of therapeutic immunosuppression. *Cryptococcus* is abundant in pigeon and chicken droppings.
8. The answer is **B**. The well-developed polysaccharide capsule of *Cryptococcus neoformans*, such as the polysaccharide capsules of many Gram negative bacteria, has anti-phagocytic properties. For this reason it is considered as the main virulence factor for this yeast.
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10. The answer is **D**. This HIV+ patient presents with *Pneumocystis carinii* pneumonia, which is best treated with high doses of trimethoprim-sulfamethoxazole administered IV. The antimicrobial properties of trimethoprim-sulfamethoxazole are related to their ability to interfere with the synthesis of nucleic acid precursors, such as dihydropteroic acid (sulfamethoxazole) and folinic acid (trimethoprim).



## Opportunistic Infections

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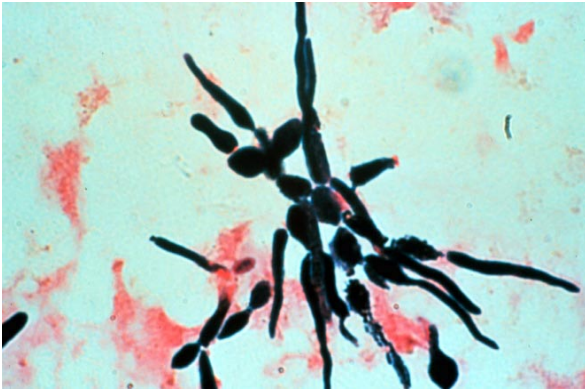
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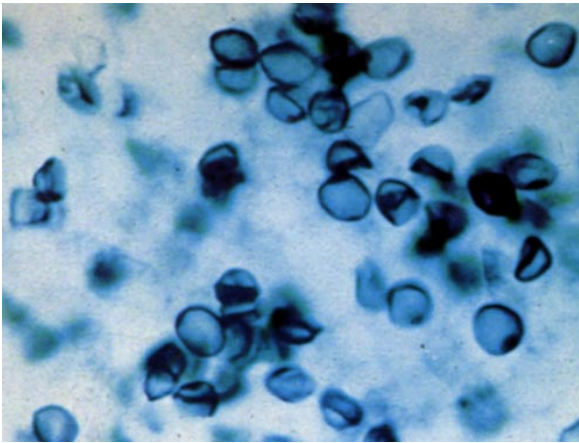
## Opportunistic Infections

### Color plates

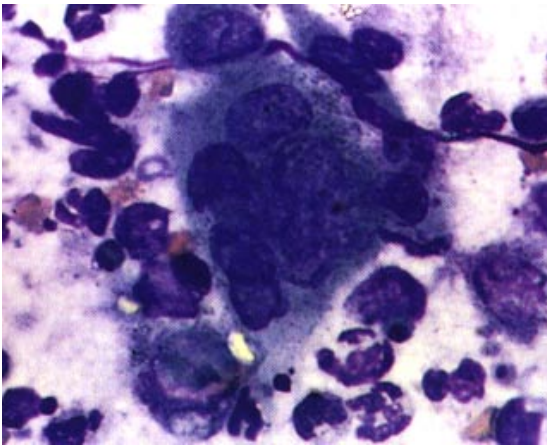
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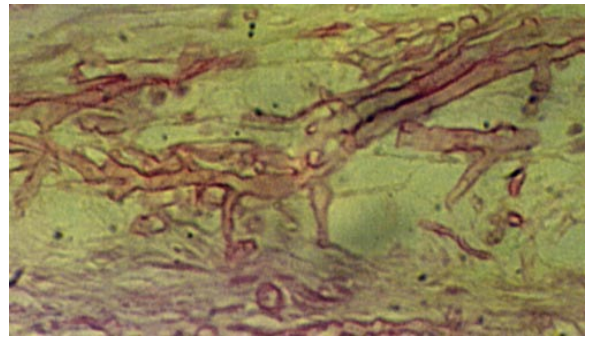
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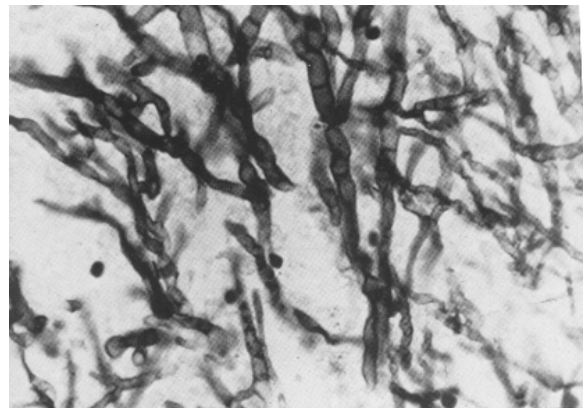
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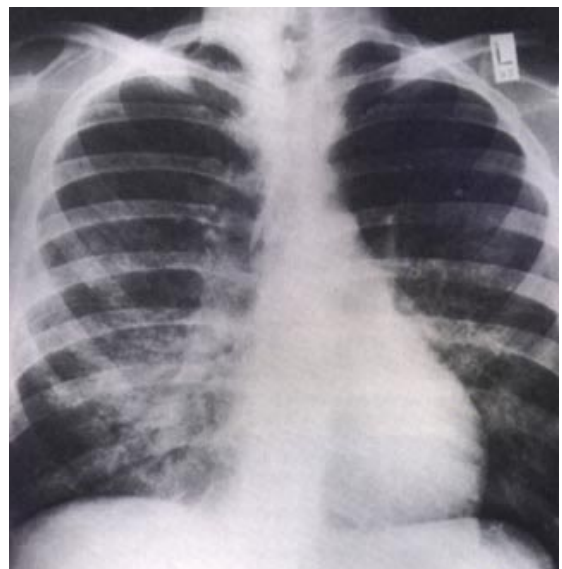
Color plate – Question 1



Color plate – Question 5



Color plate – Question 6



Color plate – Question 10